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HEALTHFUL NUTRITION AND INCREASED PHYSIC AL ACTIVITY CAN MODULATE POP TOXICIT Y THROUGH DIRECT AND EPIGENETIC REGULATORY MECHANISM S

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Introduction

Persistent organic pollutants (POPs), including dioxin-like chemicals can generate both short- and long-term health challenges for affected community members. Due to these prevalent health concerns, it is vital that public health professionals working with at-risk populations not only help monitor the ongoing health of exposed communities but also promote healthy practices and behaviors in order to prevent or reduce the potential for disease pathology. The pathologies of chronic diseases are complex and may be influenced by exposure to environmental pollutants throughout the lifespan. While a sedentary lifestyle and/or poor dietary habits can exacerbate the deleterious effects resulting from such exposure, much emerging evidence suggests that positive life-style changes (e.g., healthful nutrition, exercise) can modulate the toxicity of environmental pollutants[1,2]. Diet may serve as either an agonist or an antagonist of the health impacts associated with exposure to environmental pollutants. Thus, healthful nutrition may reduce human health risks associated with toxicant exposures and vulnerability to diseases linked to environmental toxic insults[3]. There is a significant need to further explore the paradigm of nutrition in environmental toxicology and to improve our understanding of the relationship between lifestyle modifications and toxicant-induced diseases. Factors which can trigger the pathologies of non-communicable or chronic diseases, including atherosclerosis, diabetes, and obesity, are complex. Complex diseases often do not have a single cause, and it is interaction between our genes, the environment (e.g., chemical or non-chemical stressors and/or buffers) we are exposed to and our lifestyles which ultimately cause complex diseases. Relevant environmental and lifestyle factors include the timing, from early development through adulthood, and duration of exposure to environmental toxicants, as well as potential nutritional interventions and the etiology of non-communicable diseases. Understanding mechanistic relationships among positive lifestyle changes, modulation of environmental toxicants, and susceptibility to disease development are important for both cumulative risk assessment and the design and implementation of future public health programs and behavioral interventions.

Our work has shown that diets high in anti-inflammatory polyphenols and increased physical activity are two possible strategies of modulating and reducing the toxicity of pollutants. For example, we found that animals fortified with bioactive compounds found in green tea were better prepared to counteract a subsequent exposure to dioxin-like pollutants as evidenced by decreased oxidative stress and increased antioxidant defense proteins[3]. Emerging data now implicate the importance of epigenetic control mechanisms in POP-induced inflammation. We have now shown that dioxin-like PCBs can lead to activation of the major pro-inflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) through epigenetic control mechanisms including alteration of critical histone-related proteins[5]. Also, we recently have shown that bioactive components of green tea may protect against POP-induced cellular inflammation by decreasing the activation of NFκB in part through epigenetic mechanisms[6]. Understanding the epigenetic control mechanisms of pollutant-induced disease will allow for more focused therapeutic and preventative measures which can be implemented during developmental or early phases in life and thus may be highly applicable to the fields of public health and risk assessment. The following discussion summarizes the recent literature about lifestyle modifications of POP toxicity, with a focus on sensitive biomarkers including modulation of epigenetic regulatory mechanisms.

Materials and methods

Detailed methods can be found within the references listed in this extended abstract. This extended abstract is intended to represent a review of the current literature.

Results and discussion

Exposure to POPs can be significant, especially near Superfund sites. PCBs are a model toxicant of POPs to study mechanistic relationships of chronic diseases with risks to environmental insults linked to acute or chronic exposure to POPs. PCBs are persistent and widely dispersed in the environment.

The toxicity of PCBs and other chlorinated organics may be mediated by signal transductions following receptor binding, and the myriad effects that follow as part of overall disease development. A large part of PCB toxicity has been associated with non-ortho-chlorine-substituted or so-called coplanar PCBs, which are aryl hydrocarbon receptor (AhR) ligands and inducers of CYP1A1 enzymes, and thus elicit toxic and biological responses typical of dioxin (TCDD)[1]. Many of these diseases can also be classified as inflammatory diseases, which develop over a long period of time and thus can be easily modulated by environmental exposures, specifically to POPs. There is sufficient evidence that POPs contribute to inflammation by activating oxidative stress-sensitive transcription factors such as NFκB[4]. For example, our studies suggest that PCBs, and in particular coplanar PCBs, can increase cellular oxidative stress and induce inflammatory parameters, such as inflammatory cytokines, chemokines, and adhesion molecules, in the vascular endothelium, which are metabolic events that foster an inflammatory response and the pathology of atherosclerosis[1]. Importantly, we have determined recently that exposure to dioxin-like PCBs can elicit epigenetic modifications related to activation of NFκB[5].

Epigenetic modifications of DNA and histones alter cellular phenotypes without changing genetic codes. Thus, we tested the hypothesis that endothelial cell dysfunction induced by exposure to dioxin-like PCBs is mediated in part though histone modifications[5]. Human vascular endothelial cells were exposed to physiologically relevant concentrations of several PCBs congeners (e.g., PCBs 77, 118, 126 and 153) followed by quantification of inflammatory gene expression and changes of histone methylation. Only exposure to dioxin-like PCBs 77 and 126 induced the expression of histone H3K9 trimethyl demethylase jumonji domain-containing protein 2B (JMJD2B) and activation of NF-κB signaling. The increased accumulation of JMJD2B in the p65 promoter led to a depletion of H3K9me3 repression mark, which accounts for the observed up-regulation of p65 and associated inflammatory genes. These data suggest that dioxin-like PCBs may exert endothelial cell toxicity through changes in histone modifications[5].

The paradigm of nutrition as a key factor modifying Superfund chemical (e.g., PCB) toxicity is of considerable interest to populations at risk, i.e., populations residing near Superfund sites or areas of contamination and populations with poor dietary habits. An accumulating body of evidence clearly shows that nutrition can modulate PCB toxicity[1, 3]. For example, specific fatty acids present in many oils, such as linoleic acid (the parent omega-6 fatty acid), can amplify PCB toxicity in vascular endothelial cells, an event which can be down-regulated by vitamin E[1]. Additionally, polyphenols and omega-3 polyunsaturated fatty acids have been shown to decrease toxicant-induced maladies including liver diseases, tumor formation and growth, and endothelial cell activation[1]. Our work has shown that plant-derived flavonoids such as epigallocatechin-3-gallate (EGCG), can decrease oxidative stress and inflammation, and our recent data suggest that this observed protection may be in part controlled via epigenetic mechanisms.

It is well known that bioactive food compounds such as polyphenols may exert their protection by modulating inflammatory pathways regulated through NF-κB signaling. Thus, we hypothesized that EGCG can protect against PCB-induced endothelial inflammation in part through epigenetic regulation of NF-kB-regulated inflammatory genes[6]. Human endothelial cells (EA.hy926) were exposed to dioxin-like PCB 126 and/or 15 or 30 μM of EGCG, followed by quantification of NF-kB subunit p65, histone acetyltransferase (HAT) p300 and histone deacetylases (HDACs) accumulation through ChIP assay in the promotor region of inflammatory genes. We also examined the enrichment of the acetylated H3 (ac-H3); a marker of epigenetic alterations[6]. PCB 126 exposure increased the expression of vascular inflammatory mediators, including interleukin (IL)-6, C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and IL-1α/β, which were prevented by pre-treatment with EGCG. This inhibitory effect by EGCG correlated with abolished nuclear import of p65, decreased chromatin binding of p65 and p300, as well as increased chromatin binding of HDAC1/2. Furthermore, EGCG induced hypo-acetylation of H3, which accounts for deactivation of downstream genes. These data suggest that EGCG-induced epigenetic modifications can decrease PCB-induced vascular toxicity[6].

In addition to healthful diets, exercise has also been shown to be anti-inflammatory, and an effective means of protecting against dioxin-like PCB toxicity. Our group has recently published, that in a well-studied animal model of atherosclerosis (ApoE -/-), mice exercised on a voluntary running wheel for five weeks were protected from PCB-induced alterations of systemic inflammation, glucose intolerance, and hypercholesteremia[7]. Moving forward, it will be interesting to examine if epigenetic alterations in these exercised mice mirror what was observed in the cells pretreated with bioactive polyphenols.

The role of nutrition and increased physical activity in cumulative risk assessment is being further substantiated not only as an important modulator of inflammatory and antioxidant pathways, especially associated with environmental insult, but also due to its link to the pathologies of non-communicable or chronic diseases. Diets rich in antioxidants and anti-inflammatory nutrients can improve health and decrease vulnerability to additional chemical stressors. Thus, healthy nutrition intervention may be most effective if it is considered as early in life as possible. In fact, healthful nutrition could markedly buffer the body against chemical, biological, and physical stressors that humans are exposed to on a daily basis. Thus, positive lifestyle changes, such as healthful nutrition and/or increased physical activity can potentially reduce health risks associated with exposure to hazardous substances or reduce the overall vulnerability to environmental insults.

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